The GENESIS Project (GENeralized Early Sepsis Intervention Strategies) : A Multicenter Quality Improvement Collaborative


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What is This?
The GENESIS Project (GENeralized Early Sepsis Intervention Strategies): A Multicenter Quality Improvement Collaborative

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Abstract
Background: Improved outcomes for severe sepsis and septic shock have been consistently observed with implementation of early best practice intervention strategies or the 6-hour resuscitation bundle (RB) in single-center studies. This multicenter study examines the in-hospital mortality effect of GENeralized Early Sepsis Intervention Strategies (GENESIS) when utilized in community and tertiary care settings. Methods: This study was comprised of 2 strategies to assess treatment. The first was a prospective before-and-after observational comparison of historical controls to patients receiving the RB after implementation of GENESIS in 4 community and 4 tertiary hospitals. The second was a concurrent examination comparing patients not achieving all components of the RB to those achieving all components of the RB in 1 community and 2 tertiary care hospitals after implementation of GENESIS. These 4 subgroups merged to comprise a control (historical controls treated before GENESIS and RB not achieved after GENESIS) group and treatment (patients treated after GENESIS and RB achieved after GENESIS) group for comparison. Results: The control group comprised 1554 patients not receiving the RB (952 before GENESIS and 602 RB not achieved after GENESIS). The treatment group comprised 4801 patients receiving the RB (4109 after GENESIS and 692 RB achieved after GENESIS). Patients receiving the RB (treatment group) experienced an in-hospital mortality reduction of 14% (42.8%-28.8%, P < .001) and a 5.1 day decrease in hospital length of stay (20.7 vs 15.6, P < .001) compared to those not receiving the RB (control group). Similar mortality reductions were seen in the before-and-after (43% vs 29%, P < .001) or concurrent RB not achieved versus achieved (42.5% vs 27.2%, P < .001) subgroup comparisons. Conclusions: Patients with severe sepsis and septic shock receiving the RB in community and tertiary hospitals experience similar and significant reductions in mortality and hospital length of stay. These findings remained consistent when examined in both before-and-after and concurrent analyses. Early sepsis intervention strategies are associated with 1 life being saved for every 7 treated.

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Introduction

There are more than 500,000 cases of severe sepsis and septic shock annually in the United States, with a mortality of 20% and 45%, respectively. In the last decade, hospital costs have increased 183%, faster than any cause for hospitalization with an annual cost of over $54 billion. The majority of patients with sepsis are identified in the emergency department (ED) with the remainder coming from other inpatient settings.

Improved survival rates with diseases of similar volume such as stroke, acute myocardial infarction, and trauma have been achieved through early intervention strategies comprising early detection, risk stratification, and rapid therapeutic interventions. In 2001, a similar strategy for severe sepsis and shock termed early goal-directed therapy (EGDT) resulted in an in-hospital absolute mortality reduction of 16% when compared to controls receiving standard care. Combining EGDT with other early evidence-based strategies has resulted in the creation of the sepsis resuscitation bundle ([RB] Figure 1). Over the last decade, numerous studies using a before-and-after implementation of the RB have shown similar reductions in mortality, organ failure, and health care resource consumption.

The purpose of this multicenter collaborative was to examine the impact of real-time quality initiatives in the form of GENeralized Early Sepsis Intervention Strategies (GENESIS) on in-hospital mortality, morbidity, and health care resource consumption in community and tertiary care hospitals in the United States.

Methods

Institutional Review Board Approval

The GENESIS was approved by the institutional review board at each participating center (Appendix A).

Study Setting

The GENESIS was a continuous quality improvement (CQI) initiative implemented at 5 community and 6 tertiary US hospitals. The GENESIS is comprised of a comprehensive strategy which includes (1) an institutional assessment of the sepsis prevalence and mortality, (2) identification of high-risk patients or a sepsis alert, (3) mobilization of resources, (4) timely intervention of the 6-hour sepsis bundle via a sepsis team or sepsis order sets, (5) quality indicators to assess compliance, (6) quantification of health care resource consumption, (7) assessment of outcomes, and (8) a CQI program which includes feedback and continuing education.

Study Design

Evaluation of GENESIS consisted of 2 assessment strategies. The first was a before-and-after RB implementation strategy conducted in 8 hospitals, analyzing outcomes between historical controls and patients after RB implementation. The second was to assess the impact of complete versus incomplete bundle compliance through examining a concurrent RB implementation strategy in 3 hospitals (Figure 2). These 4 groups gave rise to the control and treatment groups for comparison. The control group comprised patients not receiving the RB before implementation or group I (historical controls-IA and concurrent RB not achieved-IB). The treatment group comprised patients receiving the RB or group II (after implementation-IIA and concurrent RB achieved-IIB; Figure 2).

Participants

Patients were routinely screened in the ED, general floor (general practice unit [GPU]), operating room, and intensive

Keywords

early goal-directed therapy, resuscitation bundle, sepsis, severe sepsis, septic shock, quality improvement, emergency medicine, critical care, shock

Sepsis Resuscitation Bundle (6 - hour bundle)

1. Suspected infection:
   Confirmed or suspected source with ≥ 2 systemic inflammatory response syndrome criteria with persistent hypotension (systolic blood pressure [SBP] < 90 mm Hg or mean arterial pressure [MAP] < 65 mm Hg), lactate ≥ 4 mmol/L, vasopressor use, or organ dysfunction.
2. Serum lactate measured
3. Blood cultures obtained before antibiotic administration
4. Broad-spectrum antibiotics, from the time of presentation, administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions
5. In the event of hypotension and/or lactate ≥ 4 mmol/L (36 mg/dL)
   - Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)
   - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure > 65 mm Hg
6. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate ≥ 4 mmol/L (36 mg/dL)
   - Achieve central venous pressure of ≥ 8 mm Hg
   - Achieve central venous oxygen saturation (SvO2) of ≥ 70%
care units (ICUs) based on regional practices. Historical controls were found via chart reviews using International Classification of Diseases, Ninth Revision codes for severe sepsis (995.92) or septic shock (785.52). Inclusion criteria were a sepsis diagnosis with a lactate ≥4 mmol/L, vasopressor use, or organ dysfunction (Figure 1). Exclusion criteria were age <18 years, shock suspected secondary to cause/causes other than sepsis, or advanced directives which compromised the intended care.

Statistical Analysis
Data are presented as the mean ± standard deviation. Continuous and categorical variables were analyzed with a 2-tailed Student t test, Mann-Whitney U test, Kruskal-Wallis, or Chi-square test as appropriate. Multivariate logistic regression with risk-adjusted odds ratios (ORs) and 95% confidence intervals was conducted to eliminate confounding between variables and multiple test performance. A P value <.05 was statistically significant. Statistical analysis was performed by biostatisticians from Washington University, Henry Ford Hospital, and the University of Kansas Medical Center.

Results
The size of the community hospital beds ranged from 301 to 431 beds, with 33,000 to 95,000 annual ED visits. Tertiary hospital size ranged from 440 to 1200 beds with 46,000 to 160,000 annual ED visits.

Patient Groups
There were 6,624 patients assessed for eligibility. Due to missing mortality data, 59 (3.7%) and 210 (4.3%) patients were excluded from group I and group II, respectively. Group I, the control group (n = 1,554) consisted of patients before RB implementation or group IA (n = 952) and concurrent RB not achieved or group IB (n = 602). Group II, the treatment group (n = 4,801), consisted of patients after RB implementation or group IIA (n = 4,109) and concurrent RB achieved or group IIB (n = 692; Figure 2).
Presentation Characteristics

Group II patients were significantly older (2.8 years) and had more females (3%) and less Caucasians (5.2%) when compared to group I (all $P < .03$). Group II had a significantly higher percentage of patients originating from the ED (15.8%) and a lower percentage from the GPU (8.3%) and ICUs (7.5%; all $P < .006$). Group II also had a significantly higher temperature (0.15°C, $P < .001$). In both groups, the lung was the most common source of infection followed by urinary, gastrointestinal, blood, catheter, and other sources (Table 1).

Baseline Resuscitation Parameters and Organ Function

In group II patients, the baseline serum bicarbonate was 0.5 mEq/L higher ($P = .047$), central venous oxygen saturation [ScvO2] was 2.6% higher ($P = .01$), and lactate was 0.42 mmol/L lower ($P = .006$). There were no significant differences in the percentage of patients presenting with baseline hypotension (systolic blood pressure [SBP] <90 mm Hg or mean arterial pressure (MAP) <65 mm Hg) or baseline lactate ≥4 mmol/L between groups (Table 1). Group II baseline organ dysfunction or Acute Physiology and Chronic Health Evaluation (APACHE-II) scores were 11.2% higher ($P < .001$) and baseline Sequential Organ Failure Assessment (SOFA) scores were 12.9% higher ($P = .002$) than group I (Table 2).

Resuscitation Parameters at 6 and 24 Hours

At 6 hours, group II had a significantly higher SBP (2.7 mm Hg, $P = .047$), ScvO2 (4.4%, $P < .001$), lower lactate (0.67 mmol/L, $P = .002$), greater urine output (10.6 mL/h, $P = .023$), and greater lactate clearance (19%, $P = .044$; Table 1). No significant differences existed for MAP or central venous pressure (CVP) between groups (Table 1). At 24 hours, group II had a significantly lower heart rate (11.7 beats/min, $P < .001$), 8 mm Hg higher MAP ($P < .001$), 0.10 units lower shock index ($P = .002$), 0.7 mEq/L higher bicarbonate level ($P = .044$), 0.75 mmol/L lower lactate ($P < .001$), and 26% greater lactate clearance ($P = .003$; Table 1).

Organ Function Over the First 24 Hours

Group II APACHE-II scores significantly decreased by 15.7% compared to an 11.7% increase in group I over 24 hours ($P < .001$). Similarly, the SOFA scores significantly decreased by 15.4% in group II compared to an 18.6% increase in group I over 24 hours ($P < .001$; Table 2). The absolute improvement in organ dysfunction at 24 hours in group II compared to group I was 27.4% (APACHE-II) and 34% (SOFA).

Mortality Overall

There was a significant 14.0% absolute and a 32.7% relative risk reduction for in-hospital mortality (42.8% vs 28.8%, $P < .001$) between groups I and II. Similar and significant in-hospital mortality reductions were seen between groups IA and IIA (14%) and between groups IB and IIB (15.3%), both $P < .001$ (Figure 2 and Table 2). A cumulative examination of mortality showed a consistent decrease in mortality from 2003 to 2009 (Figure 3). Multivariate regression was used to control for baseline differences in age, sex, race, origin at presentation, temperature, bicarbonate, lactate—0 hour, ScvO2—0 hour, APACHE-II score—0 hour, and SOFA score—0 hour. Of these variables, the SOFA score—0 hour remained significantly associated with in-hospital mortality with an adjusted OR of 1.14 (1.03-1.27, $P = .01$). Overall, the treatment group (group II) had a significantly greater likelihood of death at baseline compared to those not receiving the RB (group I).

Mortality by Hemodynamic Subgroups

Group II consistently showed statistically significant lower mortalities across all hemodynamic subgroup strata of lactate levels and/or hypotension (SBP <90 mm Hg or MAP <65). Group II absolute in-hospital mortality reductions for the following subgroups were as follows (all $P < .02$): lactate ≥4 mmol/L, 18.4%; hypotensive, 17.7%; lactate ≥4 mmol/L or hypotensive, 15.7%; lactate ≤4 mmol/L and hypotensive, 22.2%; lactate ≥4 mmol/L and no hypotension, 17.9%; and lactate ≤2 mmol/L and hypotension, 5.7% (Table 2).

Mortality by Hospital Location and Type

The absolute in-hospital mortality reduction in group II versus group I for patients diagnosed in the following locations was 12.1% for the ED ($P < .001$), 15.4% for the GPU ($P = .006$), and 13.9% for the ICU ($P < .001$; Table 2). Participating centers experienced an overall absolute in-hospital mortality reduction ranging from 8.1% to 25.7% and a relative risk reduction from 21.3% to 48.9% (Table 3).

Duration of Mechanical Ventilation, Length of Hospital Stay, and Hospital Charges

Group II had significantly less mechanical ventilation (5.0%) from 0 to 6 hours ($P = .02$) and 6.2% less from 6 to 72 hours ($P = .02$). There was a 1.3-day trend toward a shorter duration of mechanical ventilation in group II ($P = .06$). There was no significant difference in mean ED length of stay. Mean hospital length of stay was significantly shorter (5.1 days) and hospital charges were $47,923 less in group II (both $P < .001$; Table 2).

Time to Completion of Therapeutic Interventions

Time to completion of interventions and reaching hemodynamic targets in group II versus group I comparisons were significantly reduced (hours) for a fluid challenge (1.18), obtaining a lactate (3.07), antibiotic administration (1.21), reaching the CVP target (2.98), and reaching the ScvO2 target (1.95; all $P < .002$). There was a trend in decreasing the time (0.77 hours) to achieving the MAP target ($P = .05$; Table 1).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group I</th>
<th>Group II</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>N = 1554</td>
<td>N = 4801</td>
<td></td>
</tr>
<tr>
<td>Total number of patients</td>
<td>1554</td>
<td>4801</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>1524 64 (17)</td>
<td>4776 62 (17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>746 48</td>
<td>2164 45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>838 82 (28)</td>
<td>2061 81 (27)</td>
<td>NS</td>
</tr>
<tr>
<td>Race, % White/Other</td>
<td>1554 75.1</td>
<td>4801 80.3</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Origin at presentation, %</strong></td>
<td>558 50.1</td>
<td>1987 65.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Emergency department</td>
<td>139 15.4</td>
<td>168 7.1</td>
<td>.006</td>
</tr>
<tr>
<td>General practice unit</td>
<td>331 34.5</td>
<td>697 27.0</td>
<td>.001</td>
</tr>
<tr>
<td><strong>SIRS characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>1070 37.1 (1.6)</td>
<td>2207 37.3 (1.6)</td>
<td>.008</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>1034 107.5 (24.7)</td>
<td>1916 109.1 (26.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>1096 24.1 (8.4)</td>
<td>2290 23.6 (8.2)</td>
<td>NS</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>1081 16.5 (14.1)</td>
<td>2228 15.9 (12.6)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Source of infection and culture results, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>208 42.5</td>
<td>492 38.7</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary</td>
<td>111 22.7</td>
<td>281 22.1</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>67 13.7</td>
<td>215 16.9</td>
<td>NS</td>
</tr>
<tr>
<td>Blood</td>
<td>43 8.8</td>
<td>98 7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Catheter</td>
<td>16 3.3</td>
<td>33 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Other sourcesa</td>
<td>44 9.0</td>
<td>153 12.0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Positive cultures that were sent, %</strong></td>
<td>336 50.4</td>
<td>656 53.2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Positive blood cultures that were sent, %</strong></td>
<td>224 37.7</td>
<td>430 38.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Laboratories—baseline, 0 hour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>235 10.9 (2.5)</td>
<td>830 11.3 (2.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet count, × 1000 per cubic mL</td>
<td>1042 230.6 (138.7)</td>
<td>1784 230.5 (137.0)</td>
<td>NS</td>
</tr>
<tr>
<td>BUN/creatinine</td>
<td>806 19.6 (11.6)</td>
<td>1846 19.1 (12.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>748 2.1 (3.5)</td>
<td>1281 1.8 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>629 2.50 (0.77)</td>
<td>1289 2.51 (0.76)</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>814 7.32 (0.15)</td>
<td>1125 7.31 (0.15)</td>
<td>NS</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L</td>
<td>690 20.5 (6.5)</td>
<td>1291 21.0 (6.0)</td>
<td>.047</td>
</tr>
<tr>
<td><strong>Baseline hemodynamic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>907 4.8 (4.1)</td>
<td>2608 4.4 (3.6)</td>
<td>.006</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>896 97.8 (27.71)</td>
<td>2287 99.6 (29.0)</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>1055 68.7 (19.9)</td>
<td>2054 69.7 (20.6)</td>
<td>NS</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>355 10.5 (6.9)</td>
<td>1096 10.8 (6.6)</td>
<td>NS</td>
</tr>
<tr>
<td>ScvO2, %</td>
<td>318 66.9 (17.0)</td>
<td>985 69.5 (13.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>1034 107.5 (24.7)</td>
<td>1916 109.1 (26.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Shock index (heart rate/systolic BP)</td>
<td>813 1.17 (0.41)</td>
<td>1902 1.16 (0.43)</td>
<td>.03</td>
</tr>
<tr>
<td>% with systolic BP &lt;90 or MAP &lt;65 (%)</td>
<td>351 56.16</td>
<td>775 51.91</td>
<td>NS</td>
</tr>
<tr>
<td>% with lactate ≥4-0 hour (%)</td>
<td>421 46.42</td>
<td>1122 43.02</td>
<td>NS</td>
</tr>
<tr>
<td><strong>6 hours hemodynamic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>414 3.84 (3.58)</td>
<td>893 3.17 (3.28)</td>
<td>.002</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>446 109.1 (23.2)</td>
<td>1014 111.7 (23.7)</td>
<td>.05</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>771 72.5 (15.3)</td>
<td>1975 73.4 (16.4)</td>
<td>NS</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>311 12.2 (5.8)</td>
<td>850 11.7 (5.1)</td>
<td>NS</td>
</tr>
<tr>
<td>ScvO2, %</td>
<td>242 69.3 (12.5)</td>
<td>740 73.8 (10.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Urine output, ml/hour (0-6 hours)</td>
<td>401 65.73 (78.0)</td>
<td>989 76.3 (80.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Lactate clearance (0-6 hours)</td>
<td>404 0.02 (1.83)</td>
<td>857 0.21 (0.87)</td>
<td>.04</td>
</tr>
<tr>
<td><strong>24 hour hemodynamic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>257 3.16 (3.01)</td>
<td>414 2.41 (2.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130 113.2 (21.3)</td>
<td>343 117.9 (21.0)</td>
<td>.03</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>409 64.8 (19.5)</td>
<td>419 72.8 (17.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>413 113.4 (26.9)</td>
<td>462 101.7 (23.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shock index (heart rate/systolic BP)</td>
<td>130 0.99 (0.31)</td>
<td>182 0.89 (0.28)</td>
<td>.001</td>
</tr>
<tr>
<td>pH</td>
<td>286 7.31 (0.15)</td>
<td>612 7.32 (0.13)</td>
<td>NS</td>
</tr>
</tbody>
</table>

(continued)
Antibiotic Administration and Culture Rates

Group II had 5.2% less antibiotic appropriateness (93.2% vs 88.1%, \( P = .004 \)) with a 2.13-day longer duration of antibiotics, \( P < .001 \). There were no differences in the overall culture and primary blood culture positivity rates between groups (Table 1).

Fluid therapy, Vasopressors, Inotropes, and Red Blood Cell Transfusions

Group II received 0.2, 0.8, and 1.1 L more fluid during the 0 to 6, 7 to 72, and 0 to 72 time periods, respectively (all \( P < .001 \)). There was no significant difference in vasopressor use during the 0- to 6-hour time period; however, there was a 15.7% absolute reduction in vasopressor use in group II over the 0- to 72-hour time period (\( P < .001 \)). There was no significant difference in the use of inotropes or red blood cell transfusions between groups (Table 1).

Analysis of Interventions on Mortality

The overall individual RB bundle element compliance was 67.5% in the concurrent group (groups IB and IIB). Obtaining a lactate (OR = 2.18, \( P < .001 \)), achieving a MAP >65 mm Hg (OR = 0.59, \( P < .001 \)), and achieving a ScvO\(_2\) >70% (OR = 0.75, \( P = .048 \)) were significantly associated with in-hospital mortality (Table 4).

Discussion

The GENESIS is associated with significantly decreased in-hospital mortality. The impact on in-hospital mortality was equally observed in a before-and-after and concurrent observational analysis based on completing the RB. These results are similar and consistent with the previous studies. These "real-life" salutary effects are seen even after inclusion of comorbidities (ie, cancer, end-stage renal, and liver disease) which could potentially diminish the treatment effect.
As with comparable diseases such as acute myocardial infarction, stroke, and trauma, a standard operating procedure that includes early detection, risk stratification, and early intervention decreases morbidity and in-hospital mortality. The 15.8% increase (from 50.1% to 65.9%) in the patients identified in the ED resulted in a significant decrease in patients diagnosed in the GPU and ICU. These patients (ICU and GPU) usually face a 3 times higher mortality risk if they develop septic shock. This earlier identification was accompanied by a significant GPU absolute in-hospital mortality reduction (48.9% - 33.5%) followed by the ICU (45.2% - 31.3%) and the ED (35.9% - 23.8%, all \(P < .001\); Table 2).

The GENESIS resulted in a significant decrease in time-to-fluid challenge, lactate measurement, antibiotic therapy, and hemodynamic target attainment. Although the total

| Table 2. Mortality, Organ Dysfunction and Health Care Resource Consumption |
|-----------------------------|-----------------------------|-----------------------------|
|                             | Group I                     | Group II                    |
|                             | N\(^a\) | Value (%) | N\(^a\) | Value (%) | Relative Risk (95% CI) | \(P\) Value |
| In-hospital mortality       |         |           |         |           |                   |         |
| Group I vs group II         | 665     | 42.8      | 1383    | 28.8      | 0.67 (0.63-0.72)     | <.001    |
| Group IA vs IIA (before vs after implementation of RB) | 409     | 43.0      | 1192    | 29.0      | 0.68 (0.62-0.74)     | <.001    |
| Group IB vs IIB (concurrent RB not achieved vs achieved) | 256     | 42.5      | 188     | 27.2      | 0.64 (0.55-0.74)     | <.001    |
| Mortality by sepsis inclusion category (at baseline) |         |           |         |           |                   |         |
| Lactate \(\geq 4\) mmol/L   | 229     | 54.4      | 404     | 36.0      | 0.66 (0.59-0.74)     | <.001    |
| SBP <90 mm Hg or MAP <65    | 243     | 47.3      | 357     | 29.6      | 0.63 (0.55-0.71)     | <.001    |
| SBP <90 or MAP <65 mm Hg or lactate \(\geq 4\) mmol/L | 362     | 47.2      | 596     | 31.5      | 0.67 (0.60-0.74)     | <.001    |
| SBP <90 or MAP <65 mm Hg and lactate \(\geq 4\) mmol/L | 222     | 48.0      | 343     | 30.4      | 0.63 (0.56-0.72)     | <.001    |
| SBP >90 or MAP >65 mm Hg and lactate \(\geq 4\) mmol/L | 203     | 42.8      | 312     | 24.9      | 0.58 (0.50-0.67)     | <.001    |
| SBP <90 or MAP <65 mm Hg and lactate \(\leq 2\) mmol/L | 286     | 52.2      | 662     | 46.5      | 0.89 (0.81-0.99)     | .02      |
| Mortality by hospital location |         |           |         |           |                   |         |
| ED                          | 208     | 35.9      | 486     | 23.8      | 0.66 (0.58-0.75)     | <.001    |
| GPU                         | 69      | 48.9      | 55      | 33.5      | 0.66 (0.50-0.87)     | .006     |
| ICU                         | 150     | 45.2      | 218     | 31.3      | 0.69 (0.59-0.81)     | <.001    |
| Mortality by centers, %     |         |           |         |           |                   |         |
| Tertiary care               | 522     | 43.2      | 1006    | 29.0      | 0.66 (0.61-0.72)     | <.001    |
| Community                   | 143     | 41.2      | 375     | 29.3      | 0.71 (0.61-0.83)     | <.001    |
| Organ dysfunction (SD)      |         |           |         |           |                   |         |
| Baseline APACHE score       | 483     | 20.6 (7.6) | 806     | 22.9 (8.0) | –                   | <.001    |
| 24-Hour APACHE score        | 482     | 23.0 (8.5) | 409     | 19.3 (7.3) | –                   | <.001    |
| Baseline SOFA score         | 406     | 7.0 (3.8)  | 299     | 7.9 (4.0)  | –                   | .002     |
| 24-Hour SOFA score          | 407     | 8.3 (4.2)  | 296     | 6.5 (3.3)  | –                   | <.001    |
| Baseline PaO2/FiO2          | 577     | 264.6 (158.6) | 820     | 262.9 (158.9) | –                   | NS       |
| 24-Hour PaO2/FiO2           | 348     | 240.7 (135.5) | 630     | 298.9 (158.2) | –                   | <.001    |
| Duration of mechanical ventilation |         |           |         |           |                   |         |
| 0-6 hours, % of patients    | 281     | 38.5      | 549     | 33.5      | –                   | .02      |
| 6-72 hours, % of patients   | 326     | 50.9      | 433     | 44.7      | –                   | .02      |
| Duration, days (SD)         | 391     | 9.7 (12.5) | 933     | 8.4 (9.8)  | –                   | .06      |
| Length of stay (SD)         |         |           |         |           |                   |         |
| ED, hours                   | 414     | 5.7 (4.5)  | 1584    | 5.4 (4.3)  | –                   | NS       |
| Hospital length of stay, days | 1554   | 20.7 (30.7) | 4809    | 15.6 (20.0) | –                   | <.001    |
| Financial costs (SD)        |         |           |         |           |                   |         |
| Hospital charges, $         | 723     | 143,949 (188 295) | 1182    | 96,026 (141 139) | –                   | <.001    |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation study; CI, confidence interval; ED, emergency department; FiO\(_2\), fraction of inspired oxygen; GPU, general practice unit; ICU, intensive care unit; MAP, mean arterial pressure; PaO\(_2\), partial pressure of arterial oxygen; RB, resuscitation bundle; SBP, systolic blood pressure; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

\(^a\) For mortality N equals the number of deaths.

As with comparable diseases such as acute myocardial infarction, stroke, and trauma, a standard operating procedure that includes early detection, risk stratification, and early intervention decreases morbidity and in-hospital mortality. The 15.8% increase (from 50.1% to 65.9%) in the patients identified in the ED resulted in a significant decrease in patients diagnosed in the GPU and ICU. These patients (ICU and GPU) usually face a 3 times higher mortality risk if they develop septic shock. This earlier identification was accompanied by a significant GPU absolute in-hospital mortality reduction (48.9%-33.5%) followed by the ICU (45.2%-31.3%) and the ED (35.9%-23.8%, all \(P < .006\); Table 2).

The GENESIS resulted in a significant decrease in time-to-fluid challenge, lactate measurement, antibiotic therapy, and hemodynamic target attainment. Although the total

![Figure 3. Cumulative mortality over the study duration.](jc.sagepub.com)
amount of fluid differed by only 1.1 L over 72 hours between groups I and II, the time to receiving a fluid challenge and meeting CVP goals was significantly reduced.\(^6\) Early and aggressive fluid administration modulates early inflammation and reduces vaso-pressor support (associated with decreased mortality) and qualification for corticosteroids.\(^{17-21,22}\) Consistent with previous studies, we found a significant association between S\(\text{Scvo}_2\), MAP, lactate measured, and mortality reduction.\(^{20,23,24}\)

Group I (control group) in-hospital mortality, in all hemodynamic subgroups, exceeded 42\% (Table 2). When compared to group II (treatment group), there was a significant in-hospital mortality reduction after receiving the RB. The in-hospital mortality for patients in this study versus the original EGDT study of Levy et al showed that a SBP <90 mm Hg or MAP \(<65\) mm Hg achieved S\(\text{Scvo}_2\) \(\geq70\)% in the control and 31.5\% versus 30.5\% in the treatment groups, respectively.\(^4\) In an examination of 15,022 patients over a similar time frame, Levy et al showed that a SBP <90 mm Hg or MAP \(<65\) mm Hg and lactate \(\geq4\) mmol/L was associated with a 46.1\% hospital mortality which corresponds to a 48.0\% observed mortality in the same subgroup in this study.\(^3\) Of particular interest are normotensive patients with an elevated lactate who are described as “cryptic shock” and who experienced an in-hospital mortality reduction from 42.8\% to 24.9\% \((P < .001).\(^{25}\) These patients who appear stable by traditional vital signs have an underappreciated illness severity and often later suffer cardiopulmonary collapse or multiorgan failure due to persistently untreated hypoperfusion.\(^{26,27}\)

Despite significantly higher baseline organ dysfunction scores (APACHE-II and SOFA) in group II, there was still a significantly greater improvement over the first 24 hours indicating improved organ function compared to group I. For example, while baseline pulmonary function via partial pressure of arterial oxygen/fraction of inspired oxygen \((\text{Pa}O_2/\text{Fi}O_2)\) ratios were equal, group I significantly worsened by 9.0\% while group II improved by 13.7\% at 24 hours (both \(P < .001)). Paralleling these findings were a lower use of mechanical ventilation in group II. Early detection and treatment of shock on hospital admission are associated with decreased need for mechanical ventilation.\(^{27}\)

Lactate clearance is significantly associated with the modulation of inflammatory biomarkers, organ failure, and outcome.\(^{28}\) In this study, the lactate clearance in group I versus group II significantly improved over the first 6 hours (2\% vs 21\%, \(P = .044)) and over 24 hours (11\% vs 39\%, \(P < .001)). However, the alacemic patients (lactate \(<2\) mmol/L with hypotension) had a baseline in-hospital mortality of 52.2\% and were less responsive to the in-hospital mortality reduction of

### Table 3. Individual Study Center Settings and Mortalities\(^a\)

<table>
<thead>
<tr>
<th>Center</th>
<th>Hospital Locations</th>
<th>Group I Period</th>
<th>Group II Period</th>
<th>Group I Mortality</th>
<th>Group II Mortality</th>
<th>Absolute Mortality Reduction</th>
<th>Relative Mortality Reduction</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>ED/GMF/OR/ICU</td>
<td>2003-2005</td>
<td>2006-2007</td>
<td>43.0</td>
<td>33.6</td>
<td>9.5</td>
<td>22.0</td>
</tr>
<tr>
<td>B</td>
<td>ED/ICU</td>
<td>2006</td>
<td>2007-2009</td>
<td>36.7</td>
<td>28.6</td>
<td>8.1</td>
<td>22.1</td>
</tr>
<tr>
<td>C</td>
<td>ED/ICU</td>
<td>2004</td>
<td>2005-2007</td>
<td>35.3</td>
<td>27.8</td>
<td>7.5</td>
<td>21.3</td>
</tr>
<tr>
<td>D</td>
<td>ED/ICU</td>
<td>2005</td>
<td>2006-2008</td>
<td>41.3</td>
<td>25.3</td>
<td>16.0</td>
<td>38.7</td>
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<tr>
<td>E</td>
<td>ICU</td>
<td>2004-2005</td>
<td>2006-2007</td>
<td>41.6</td>
<td>31.8</td>
<td>9.8</td>
<td>23.6</td>
</tr>
<tr>
<td>F</td>
<td>ED/GMF/OR/ICU</td>
<td>2003-2005</td>
<td>2006-2009</td>
<td>38.8</td>
<td>30.7</td>
<td>8.1</td>
<td>20.8</td>
</tr>
<tr>
<td>G</td>
<td>ED/ICU</td>
<td>2004-2004</td>
<td>2005-2008</td>
<td>36.8</td>
<td>18.8</td>
<td>18.0</td>
<td>48.9</td>
</tr>
<tr>
<td>H</td>
<td>ED/GMF/ICU</td>
<td>2003-2004</td>
<td>2005-2008</td>
<td>55.9</td>
<td>30.2</td>
<td>25.7</td>
<td>46.0</td>
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<tr>
<td>I(^b)</td>
<td>ED/GMF/ICU</td>
<td>2005-2008</td>
<td>56.3</td>
<td>40.0</td>
<td>16.3</td>
<td>28.9</td>
<td>41.5</td>
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<td>J(^b)</td>
<td>ED/GMF/OR/ICU</td>
<td>2005-2008</td>
<td>36.5</td>
<td>21.4</td>
<td>15.1</td>
<td>41.5</td>
<td>41.5</td>
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<tr>
<td>K(^b)</td>
<td>ED/GMF/OR/ICU</td>
<td>2006-2009</td>
<td>43.0</td>
<td>23.2</td>
<td>19.8</td>
<td>46.0</td>
<td>46.0</td>
</tr>
</tbody>
</table>

Abbreviations: ED, emergency department; GMF, general medical floor; OR, operating room; ICU, intensive care unit.\(^a\) The identity of the hospitals are blinded.\(^b\) Concurrent centers.

### Table 4. Adjusted Predictors of Mortality—Early Therapeutic Interventions

<table>
<thead>
<tr>
<th>Therapeutic Interventions</th>
<th>Variable in Database</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Hour resuscitation bundle</td>
<td>Lactate—0 hours</td>
<td>2.18</td>
<td>1.89-2.52</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood cultures before antibiotics</td>
<td>Blood culture in (&lt;3) hours</td>
<td>1.01</td>
<td>0.84-1.21</td>
<td>.92</td>
</tr>
<tr>
<td>Early treatment with antibiotics</td>
<td>Antibiotics in (&lt;3) hours</td>
<td>1.00</td>
<td>0.85-1.18</td>
<td>.96</td>
</tr>
<tr>
<td>Intravenous fluids delivered</td>
<td>Fluid challenge in (&lt;3) hours</td>
<td>1.26</td>
<td>0.96-1.66</td>
<td>.09</td>
</tr>
<tr>
<td>Mean arterial pressure (\geq65) mm Hg achieved</td>
<td>MAP (\geq65) mm Hg—6 hours</td>
<td>0.59</td>
<td>0.50-0.70</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Central venous pressure (\geq8) mm Hg achieved</td>
<td>CVP (\geq8) mm Hg—6 hours</td>
<td>1.17</td>
<td>0.88-1.57</td>
<td>.28</td>
</tr>
<tr>
<td>Central venous oxygen saturation (\geq70)% achieved</td>
<td>S(\text{Scvo}_2) (\geq70)%—6 hours</td>
<td>0.75</td>
<td>0.56-0.99</td>
<td>.047</td>
</tr>
</tbody>
</table>

Abbreviations: CVP, central venous pressure; MAP, mean arterial pressure; S\(\text{Scvo}_2\), central venous oxygen saturation.
GENESIS than any other hemodynamic subgroup. This alactic patient population raises caution with the use of lactate clearance as an isolated diagnostic and therapeutic end point.

There was a 24.6% reduction in duration of hospital stay and a 33.3% reduction in total hospital charges per admission following GENESIS implementation which are similar to the previous reports. Ross et al found that the association between hospital volume and 30-day mortality is maximized when the volume threshold for hospitalization exceeds 210 patients per year for pneumonia in particular. Applying this economic model to our study means that 1071 hospital days could potentially be saved resulting in $10,063,830 in-hospital charges saved per year.

Limitations
This study was not a prospective randomized trial, thus, it has the capacity to reveal associations but not causal relationships. Additional unmeasured procedural changes at institutions, such as implementation of other quality initiatives, may have led to unaccounted differences between groups over time. These include other components of sepsis management in the subsequent 24 hours such as corticosteroids, protective lung strategies, glucose control, recombinant activated protein C, gastrointestinal ulcer, and deep venous prophylaxis. These interventions (some debatable) and the diagnostic coding for sepsis have seemingly diminished mortality over the last decade. In addition, despite the use of consistent criteria for identifying patients with severe sepsis and septic shock, variability in diagnosis, and chart abstraction may have led to heterogeneity in historical controls. The designation of patients into control and treatment groups was based on assumptions of care or the treatment effect. The control group patients not receiving or achieving the RB (Group IA and IB) could have received partial RB completion. The treatment group or patients receiving the RB (Group II A) could have received less than full RB completion. Group IIA in particular was assumed to have the same intervention as group IIB; however, despite the lack of quantification of bundle compliance for group IIA, it is likely they received less than 100% RB compliance, given that the overall concurrent model averaged 67% compliance between fully achieved and not fully achieved cohorts.

In either scenario regarding the control or treatment groups, the overall treatment effect of the study and findings of this study are conservative and understated. Although there is a 4-fold greater number of patients in the before-and-after group compared to the concurrent group, the findings are comparable. Baseline illness severity and mortality were similar across all 4 subgroups. The similar mortality reduction seen in both assessment strategies indicate that the treatment effect of the RB is very robust. Because of incomplete data capture, the post hoc detail of which bundle element is most important remains unconfirmed.

Despite these aforementioned issues, this is the first study to show similar in-hospital mortality reductions in both a before-and-after and concurrent implementation designs. The concurrent findings emphasize the importance of RB compliance and CQI to realize improved outcomes. These findings also support the notion that implementation trials can be scientifically acceptable alternatives to randomized controlled trials. From the standpoint of equipoise in following sepsis guidelines, this study design avoids the ethical issue of randomization to potentially inferior care that is not in accordance with current best practice recommendations.

Conclusions
Patients with severe sepsis and septic shock receiving RB within community and tertiary care settings experience significant reductions in in-hospital mortality, organ dysfunction, and health care resource utilization. This results from early detection of high-risk patients, a reduction in time to delivery of critical elements of best practice care, and a CQI process. Future emphasis should be directed to overcoming logistical, institutional, and professional barriers to the implementation of RB similar to the approaches for acute myocardial infarction, stroke, and trauma. In doing so, this may lead to at least 1 life being saved for every 7 patients treated for severe sepsis and septic shock.
## Appendix A

### Table A1. GENESIS Participating Members

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The authors Cannon, Holthaus, Posa, Gunaga, Turman, Weingarten, Suarez, and Rivers were involved in the study conception and design, coordination, data collection, statistical analyses, interpretation of the data and results, manuscript preparation, approval and overall responsibility for the contents of the manuscript. The authors Zubrow, Kella, Elkin, Davis, Milling, Lidsky, Coba, and Yang were involved in the study coordination, data collection, interpretation of the data and results, manuscript preparation, and approval of the manuscript. This research has been presented at the (1) Society of Critical Care Medicine Annual Congress in Nashville, Tennessee and received Annual Scientific Award for Top Ten Abstracts, 2009. (2) Mediterranean Emergency Medicine Congress in Valencia, Spain and received the Best Abstract Award, 2009. (3) American College of Emergency Physicians, Boston, Massachusetts in 2009. (4) International Conference on Emergency Medicine, Singapore and received the Best Oral Presentation Award, 2010.

Declaration of Conflicting Interests
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